

Critical Review

Use of acupuncture to alleviate side effects in radiation oncology: Current evidence and future directions

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Received 2 May 2016; received in revised form 30 July 2016; accepted 3 August 2016

Abstract

Several reports have shown that acupuncture is an effective method of complementary medicine; however, only a few of these reports have focused on oncological patients treated with radiation therapy. Most of these studies discuss a benefit of acupuncture for side-effect reduction; however, not all could demonstrate significant improvements. Thus, innovative trial designs are necessary to confirm that acupuncture can alleviate side effects related to radiation therapy. In the present manuscript, we perform a broad review and discuss pitfalls and limitations of acupuncture in parallel with standard radiation therapy, which lead the way to novel treatment concepts.

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Introduction

Complementary and alternative medicine (CAM), including acupuncture, homeopathy, naturopathy, and special dietary concepts, is gaining more and more interest. Many patients ask for CAM methods to enhance

the efficacy of their cancer treatment, to boost their immune system, and to reduce side effects and increase tolerability of conventional cancer care.¹⁻³ Several methods of Traditional Chinese Medicine (TCM) are subclassified as CAM, and acupuncture is 1 of the most frequently requested and offered treatments. Thus, there is a need for solid data on the effects of acupuncture, and several prospective approaches are currently being defined. Acupuncture is a well-established part of TCM and 1 of the oldest treatments. It has been practiced in China and other Asian countries for more than 2000 years. Meanwhile, reported clinical outcomes in scientific

Conflicts of interest: None.

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<http://dx.doi.org/10.1016/j.adro.2016.08.002>

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and nonscientific media have convinced at least subgroups of physicians about the positive effects.

According to the theory, “energy” (Qi) flows along predefined “pathways” (meridians) in our human body and influences health and well-being. The total balance of this “flowing energy” is defined as the optimal state and is characterized as being “healthy.” Various stressors including sleeping disturbances; poor work-life balance; or illnesses such as infections, cancer, or chronic diseases can trigger an imbalance within these specified meridians.

From the classic acupuncturist’s point of view, achieving a healthy energy flow within the meridians is the starting point for every therapeutic intervention. The technique is based on stimulating predefined acupuncture points (acupoints) along these meridians using needles, slight pressure, ultrasound, or laser, for a certain duration once or several times per week. There is strong knowledge about the location of these acupoints in correlation to the human anatomy, and experienced therapists not only require a solid repertoire of anatomical structures but need also manual experience in finding the respective acupoints and placing the needles. In general, for certain targeted symptoms, corresponding acupoints exist. By choosing the acupoints wisely and applying well-trained acupuncture, the idea is to restore the unbalanced energy, which can result in symptom reduction and/or relief of suffering.

Scientific investigation of the positive effect of acupuncture exist for some disease conditions, such as lower back pain, sinusitis, fatigue, and headache.^{1,2,4-17} However, for acupuncture, the ideal comparator has not been found, which could be sham acupuncture or an acupuncture-free control arm, such as palliative or supportive care. Only a few studies have been conducted in the field of radiation oncology and are summarized in the present manuscript. In the literature, for instance, comprehensive reviews on the effect of acupuncture on cancer-related fatigue exist.¹⁸⁻²⁰ Most reports only include few patients. Large randomized trials have not been initiated. Nevertheless, many practitioners are offering acupuncture to cancer patients receiving radiation therapy (RT), independently of the lack of clinical data.

We, therefore, reviewed all existing data from prospective trials on acupuncture in radiation oncology and discuss potential benefits, downsides, and rationales for future prospective clinical trial designs.

Methods and materials

We performed a literature search in PubMed with the following search query: (acupuncture[Title/Abstract] AND (study[Title/Abstract] OR trial[Title/Abstract]) AND (radiation[Title/Abstract] OR radiotherapy[Title/Abstract] OR chemorad*[Title/Abstract]) AND humans [Filter]) NOT review[Publication Type]. The search

revealed 54 citations, which were screened manually by 2 clinical scientists with special experience in CAM (S.C. and R.A.). Only articles fulfilling the following requirements were included in this review: (1) patients treated with RT, (2) acupuncture implemented to alleviate symptoms or side effects from RT, and (3) randomized prospective trial.

We identified 10 articles with the abovementioned terms. Of those, 2 were feasibility studies for subsequent larger trials. All were from university-based centers with special institutions focusing on CAM treatments. Because of the small number of trials and subsequently the small number of patients included in these trials, we chose a trial-by-trial comparison method. Trial designs, as well as statistical methods, were very heterogeneous, and the chosen endpoints included well-measurable items such quality of life (QoL) or patient-reported reduction/improvement of side effects (eg, fatigue, xerostomia). A summary of these trials is shown in [Table 1](#).

References were selected and managed with an EndNote library version X7.5 (Thomson Reuters, Toronto).

Results

Ten articles were found in the literature reporting on randomized acupuncture trials in the context of radiation oncology ([Table 1](#)). Targeted symptoms and endpoints varied between trials.

Xerostomia

In 5 trials, xerostomia was chosen as an endpoint. Patients with RT treatment in the head and neck region were included in these trials. Four of the 5 studies demonstrated a significant reduction of xerostomia by additional acupuncture. In 1 study, xerostomia was also reduced in the control arm applying placebo acupuncture.

The study by Blom et al²¹ evaluated 38 patients with radiation-induced xerostomia, of which 20 were treated with classic acupuncture in the experimental arm and 18 patients received superficial acupuncture as placebo in the control arm. In both groups, patients showed significantly increased salivary flow rates after acupuncture treatment. The results indicate that among the patients who already had increased salivary flow rates after the first 12 acupuncture sessions, the majority had a high probability of continual improvement after the completion of acupuncture treatment. The improved salivary flow rates usually persisted during the observation year.

Radiation-induced xerostomia was also addressed in the study by Cho et al²² for head and neck cancer patients. Here, 12 patients were included in the trial and randomized into two groups. The standard arm consisted of sham acupuncture, the experimental arm included 4 acupoints

Table 1 Studies evaluating acupuncture to alleviate radiation-related side effects in cancer patients

No.	Study	Year of publication	No. of patients	Target symptom	Needlepoints	Endpoint
1	Blom et al ²¹	1996	38	Xerostomia	Du 20, St 7, Si 17, Li 18, St 3, St 5, St 6, P 6, H 7, Li 11, Li 10, Li 4, Si 3, St 36, Liv 3, Sp 8, Sp 6, Ki 7, Ki 3, Ki 5, Sp 3	Improvement, no significance; improvement also in placebo group
2	Cho et al ²²	2008	12	Xerostomia	St 6, Li 4, St 36, Sp 6	Significant improvement
3	Balk et al ²⁰	2009	27	Cancer-related fatigue	Li 4, Ren 6/CV 6, Sp 6, Ki 3, St 36	Improvement
4	Enblom et al ²³	2011	109	Emesis	PC 6	Improvement with sham and verum acupuncture compared with standard care
5	Enblom et al ²⁴ (feasibility trial)	2011	10	Nausea	PC 6	Suggested benefit of verum
6	Enblom et al ²⁵	2012	215	Nausea	PC 6	No difference between verum and sham
7	Meng et al ²⁶ (feasibility trial)	2012	23	Xerostomia	Ren 24, LU 7, K 6, Shenmen, Point Zero, SG 2, Larynx	Significant reduction of xerostomia and improvement of QoL compared with sham acupuncture
8	Meng et al ²⁷	2012	86	Xerostomia	Ren 24, LU 7, K 6, Shenmen, Point Zero, SG 2, Larynx	Significant reduction of xerostomia and improvement of QoL compared with sham acupuncture
9	Lu et al ²⁸	2012	42	Dysphagia	GV 24, GV 20, I 16, GB 20, SV 24, SV 23, ST 7, St 6, St 5, LI 2, LI 11, ST 36, SP9, SP6, K3, Yintang	Ongoing
10	Simcock et al ²⁹	2013	145	Xerostomia	LI 12; LI 20; Salivary Gland 2, Modified Point Zero, Shen Men	Significant improvement than standard oral care

(St 6, Li 4, St 36, S 6). Acupuncture was performed twice weekly for 6 weeks. Needle points were chosen for the efficacy on the respective meridians in promoting salivary flow or water-like elements of the body. A minimum dose exceeding 38 Gy and an exposed volume of the parotid gland >50% were inclusion criteria. Endpoints were nonstimulated and stimulated saliva flow, as well as QoL assessed by a xerostomia questionnaire (XQ), an 8-item survey by the MD Anderson Symptom Inventory Head-and-Neck. Results showed no statistical difference between both groups regarding saliva flow; however, real acupuncture increased saliva flow and showed improved symptoms in the XQ scores.

The Shanghai Group from Fudan University published 2 trials.^{26,27} First was a feasibility study followed by a prospective randomized trial, both with the target symptom xerostomia. The feasibility study was planned to determine whether a randomized trial with sham

acupuncture as a comparator was practicable. Since the data showed a significant increase in QoL and reduction of xerostomia, they launched a larger trial with the same acupoints (Table 1). In this trial, 86 patients were randomized into 2 groups, 40 in the acupuncture arm and 46 in the sham acupuncture arm. Endpoints of the study were QoL assessed by the XQ and stimulated and unstimulated salivary flow rates. QoL revealed a significant improvement in the verum group compared with the sham group, and salivary flow measurements demonstrated a significantly higher rate in the acupuncture group in the early phase at week 3 and also during longer follow-up at 1 and 6 months. Thus, the team from Fudan University could demonstrate that acupuncture works as an excellent strategy to alleviate side effects.

The research group from Sussex compared acupuncture with oral care in patients with chronic xerostomia

after RT for head and neck cancer.²⁹ Seven oncology centers in the United Kingdom participated. Inclusion criteria consisted of prior RT (at least 18 months) with at least 1 parotid in the target volume (without any dose constraints). The study used a crossover design beginning 4 weeks after the end of the first intervention (acupuncture vs oral care) was used. Acupuncture was performed weekly for 8 consecutive weeks with a duration of 20 minutes per session. Oral care included dietary approaches, symptomatic relief products such as artificial saliva, and oral hygiene advice. Primary and secondary endpoints were the patient-reported change in severity of xerostomia, xerostomia-related symptoms, stimulated and unstimulated saliva production, and QoL. The results showed that 5 symptoms improved significantly after acupuncture compared with oral care. The difference was significant at $P = .0031$ for improvement of xerostomia, adjusted for time, residual effects, patients' characteristics, and treating center. However, saliva measurement was unchanged between both groups.

Cancer-related fatigue

Balk and colleagues²⁰ performed a pilot study as a randomized modified, double-blinded, placebo-controlled trial of acupuncture for cancer-related fatigue. A total of 54 patients were included who had surgery alone or in combination with chemotherapy with an indication for RT. The standard arm consisted of acupuncture once or twice per week for 4 weeks. Needles were placed unilaterally or bilaterally depending on the acupoints. The control arm consisted of sham acupuncture mimicking true acupuncture. Of the 27 patients recruited and randomized into the verum arm, only 26 completed treatment. Results showed that patients' fatigue in the verum acupuncture group had a better improvement than in the control arm. Other endpoints, including physical and mental distress and QoL, improved during treatment as well; however, not significantly between both groups. The study showed a clear benefit for acupuncture in terms of fatigue reduction.

Nausea and emesis

Three trials from the same group attempted to reduce nausea or emesis by adding acupuncture to RT. Enblom et al²³ present a trial with 267 patients, of which 109 were randomized to verum, 106 patients to sham acupuncture, and 62 patients were treated with standard care. Patients included received RT in the abdominal/pelvic region. Endpoints were mainly clinical data on nausea and nausea-related symptoms. Nausea was lower in the acupuncture cohort (37%) compared with the standard care cohort (63%). Almost all patients expected a large

antiemetic effect; however, no difference between verum and sham acupuncture could be observed.

The same group performed a randomized controlled trial comparing placebo acupuncture versus verum acupuncture, again for radiation-related nausea.²⁵ Before starting the study with 215 patients, a pilot study with 10 patients was conducted.²⁴ Verum and sham acupuncture was delivered close to (before or after) the first RT session for 30 minutes, 3 times per week for the first 2 weeks, then twice weekly for the remaining course of RT. Endpoints were an emesis questionnaire; weekly "open questions" on different aspects such as mood, sleep, or pain; as well as evaluation of the treatment protocol including patients' sensations at needle insertion. Verum acupuncture was not proven to be more effective than sham acupuncture in reducing radiation-induced nausea; however, patients in both groups had a significant benefit in terms of nausea reduction.

Dysphagia

Dysphagia is a common side effect in patients treated with RT in the head and neck region. This symptom is very distressing for the patients, not only because of the pain but also because of the subsequent difficulty in eating, drinking, and swallowing. One randomized, sham-controlled trial focused on dysphagia and the benefit of acupuncture on symptom reduction published by Lu et al.²⁸ The team examined patients after radiation chemotherapy for head and neck cancer. A total of 42 patients were included. Endpoints of the included changes in the MD Anderson Dysphagia Inventory Score from baseline to 12 months. The secondary endpoint was QoL. A subgroup of patients received testing for salivary flow rates and cytokines, including plasma transforming growth factor and interleukin, to identify a biological explanation for any changes observed. The final results of the study have not yet been published; however, the trial design is promising to support the use of acupuncture for relief of dysphagia in head and neck cancer patients.

Discussion and future trial design

The present article summarizes all relevant studies available on the effect of acupuncture to reduce radiation-related side effects. Because acupuncture is discussed controversially, several groups have designed such trials to define the value of acupuncture in modern radiation oncology. The primary aim of all trials was to demonstrate that verum acupuncture has the potential to reduce common side effects, including fatigue or xerostomia, in patients treated with radiation therapy. Generally, more data are available on patients treated with chemotherapy of other oncological treatments; however, few data are available for patients treated with RT.

Several groups have shown (significant) symptom reduction with acupuncture concomitant to RT. All studies have shown that acupuncture is associated with better outcome in relieving disorders than the control groups.^{20-25,29} This effect is observed in the verum acupuncture and in the sham acupuncture arms at least in 3 trials. The group of Meng and coworkers demonstrated a significant benefit of verum acupuncture compared with sham acupuncture.^{26,27} One trial is still ongoing²⁸; thus, controversial data exist and further clarification is required.

Acupuncture has consistently shown a benefit; difficulties were observed when compared with sham acupuncture, because in these groups symptom improvement was also observed. In the study by Blom et al,²¹ improvement in salivary flow and other attempted effects of acupuncture were observed also in the placebo group. Thus, they clearly recommend using acupuncture treatment with less sensory effect and subsequently reduced stimulation in the control arm. This conclusion has also been published by other groups^{8,30}; however, it stands in contrast to data on sham acupuncture according to the trials by Sertel et al,^{1,4} who reported the overall feasibility of their sham acupuncture concept and showed a significant benefit of real acupuncture for several disease groups, including nasal congestion and posttonsillectomy pain. Explanations for this effect may be that sham acupuncture also releases some triggers and stimulates in spite of not being placed at dedicated acupoints. Activation of limbic regions by tactile stimulation is known, and sham needles have been observed to activate a variety of brain areas depending on the needle and stimulation used.^{31,32} Other explanations might be that some therapists talk to patients longer and have more body contact, which itself can reduce psychological distress.³³⁻³⁵ Because psychological distress can be a predictor of emesis, nausea, or other symptoms, reduction of stress can lead to symptom improvement. Kaptchuk and coworkers have addressed this issue and confirmed that the patient-therapist interaction is more important than the needle stimulation itself.³⁶⁻³⁸ This argues for standardized interaction between both treatment groups in a prospective randomized trial.

White et al published a cumulative review on acupuncture-related side effects and reported serious side effects at 0.05 per 10,000 patients treated.³⁹ Most adverse events were related to improper use of the acupuncture needles or improper application, mostly in series where patient self-application were evaluated, although the studies assert that patients were trained by experienced therapists.⁴⁰⁻⁴² Leung et al reported that most events observed are not adverse events, but treatment-related side effects from wrong handling or application. Thus, the authors conclude, such events are clearly preventable.^{42,43}

Zhuang et al⁴⁴ searched for evidence focused on xerostomia reduction by acupuncture in head and neck cancer patients. From the data available, they concluded that insufficient evidence is available to judge whether acupuncture is safe and whether it is effective in preventing or treating radiation-induced xerostomia. Significant research remains to be done before acupuncture can be recommended for routine use in radiation-induced xerostomia.⁴⁴ We searched for all trials on acupuncture and RT, and at least 5 randomized controlled trials exist in this context. Of those, 3 almost consistently showed a benefit for acupuncture compared with sham acupuncture, “usual care” within the study center, or wait and see without any treatment.^{20,22-26,28,29}

Is there a way to fully assess the effect of acupuncture? A close look at the studies (Table 1) reveals small patient numbers and heterogeneous patient collectives. Moreover, if an effect on radiation-related symptoms is the focus, dose constraints to the responsible organs as well as the implementation of modern RT techniques are important prerequisites. Indeed, the different studies are not easy to compare with each other because of variable selected control groups. Endpoints should include patient-reported subjective reporting, but also objective measurements. For xerostomia assessment, unstimulated and stimulated saliva flow measurements are certainly helpful; however, dose constraints to salivary glands and selective dose sparing of salivary glands, if oncologically feasible, would be an important complement. To boost evidence, we have to offer acupuncture in a larger population-based approach. Sham acupuncture control arms seem to be a valid comparator, and the Shanghai group has shown that this can work effectively in a prospective randomized trial.²⁷ Other groups have also supported this evidence, but not necessarily with cancer patients but with post-mastectomy pain, sinusitis, or osteoarthritis.^{1,4,6,7} In this analyses, not only patient-reported outcome measures showed improvement, but also standardized measures (eg, lung function in the study on postmastectomy pain).⁶ As a comparator, sham acupuncture was implemented. In those arms, every patient also received an acupuncture treatment, but the needles were not inserted as deeply as in real acupuncture and the acupoints did not lay on the traditional given “pathways.”

A conclusion from all studies, independent of RT treatment, is that acupuncture is considered a safe treatment without any severe side effects. Several reports including extensive reviews have confirmed this. Acupuncture has the potential to reduce side effects and enhance QoL when applied by an experienced therapist and in conjunction with high-end modern medicine.

As a general rule of acupuncture in cancer care, the conclusion must be that acupuncture is becoming more and more popular as an asset in oncology, even though there are many aspects that need to be addressed and standardized, ideally within prospective clinical trials.⁴⁵

For radiation oncology, we can support this conclusion; however, we must add that standardized parameters for RT as well as information on dose application need to be established. At the Technical University of Munich, Department of Radiation Oncology, we are currently in the process of implementing such trials, and the first study evaluating the effect of acupuncture on fatigue and QoL related to RT based on a sham acupuncture comparator is the first in line (**R**andomized **d**ouble-blind study to **e**valuate the efficacy of acupuncture compared to sham-acupuncture to ameliorate radiation-related side effects [ROSETTA] Trial).

Conclusion

A few small studies have assessed the benefit of acupuncture against radiation-related side effects. Most have shown a benefit; however, most include only small numbers of patients and a variety of endpoints. Keeping in mind that acupuncture has been used in TCM for thousands of years, some benefits can be expected, and it is our task in modern oncology to examine and prove these effects. Thus, innovative trial designs and selection of appropriate patient cohorts for CAM methods will help define the role of acupuncture in modern oncology.

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